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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/040,128

01/02/2002

Fang Liao

11245/46902

8763

26646 7590 01/31/2007  
KENYON & KENYON LLP  
ONE BROADWAY  
NEW YORK, NY 10004

EXAMINER

RAWLINGS, STEPHEN L

ART UNIT

PAPER NUMBER

1643

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/31/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/040,128	<b>Applicant(s)</b> LIAO ET AL.	
	<b>Examiner</b> Stephen L. Rawlings, Ph.D.	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 13-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 March 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>20050308</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. The amendment filed February 24, 2005, is acknowledged and has been entered. Claims 1 and 12 have been amended.

2. Claims 1-22 are pending in the application. Claims 13-22 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 10, 2004.

3. Claims 1-12 are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Information Disclosure Statement***

5. The information disclosure filed March 3, 2005, has been considered. An initialed copy is enclosed.

#### ***Election/Restrictions***

6. Claims 8 and 9, which were previously withdrawn from further consideration, have been considered herein with claims 1-7 and 10-12. Accordingly, the inventions of Groups I, II, III, and IV (which were rejoined by the preceding Office action mailed August 24, 2004) have been rejoined with the inventions of Group V; and to that extent that the restriction and election requirement set forth in the Office action mailed November 10, 2003, has been withdrawn.

#### ***Drawings***

7. The replacement drawings filed February 24, 2005, are acceptable.

***Grounds of Objection and Rejection Withdrawn***

8. Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed August 24, 2004.

***New Grounds of Objection and Rejection***

***Specification***

9. The abstract of the disclosure is objected to because it is entitled "Abstract of the Invention", where it should be entitled "Abstract" or "Abstract of the Disclosure". Correction is required. See MPEP § 608.01(b).

10. The disclosure is objected to for the following reason:

At paragraph [0094] of the published application<sup>1</sup>, the specification teaches antibody E4B9 binds to an epitope of *murine* (i.e., mouse or rat) VE-cadherin, which is contained in the amino acid sequence of "peptide 1" sharing 100% homology with human VE-cadherin. At paragraph [0028] the specification describes "peptide 1" as having the following amino acid sequence: DEIWNQMHHIDEKNE-Cys. This disclosure explains that the carboxy-terminal cysteine was added to the amino acid sequence of the native peptide to facilitate KLH-coupling. Therefore, it would be understood that "peptide 1" is the amino acid sequence of mouse or rat VE-cadherin; however, according to Figure 2, mouse VE-cadherin and human VE-cadherin do not comprise the amino acid sequence of "peptide 1", but rather comprise amino acid sequences that differ from this sequence by one or two amino acids: DWIWNQMHHIDEKNE and DWIWNQMHHIDEKNT, respectively.

Appropriate correction, so as to resolve the apparent incongruity of these various disclosures, is required.

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<sup>1</sup> U.S. Patent Application Publication No. 2002/0160003 A1.

***Claim Rejections - 35 USC § 112***

11. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-6, 8, and 10-12 are indefinite because claim 1 recites, “a site on a VE-caderin, said site being within the about first 15 N-terminal amino acids of domain 1 of a VE-cadherin and said N-terminal amino acids having an insertion, deletion or substitution of from 1 to about 5 amino acids relative to a native VE-cadherin amino acid sequence”. According to the claim the antibody or antibody fragment binds a site on a VE-cadherin. Consistently, the site on a VE-cadherin to which the claimed antibody or antibody fragment binds is contained within a portion of a VE-cadherin. However, inconsistently, the claim further recites the site is contained within a portion of the VE-cadherin, which differs from the corresponding portion of “native VE-cadherin”. Does the antibody bind VE-cadherin, or not? Given the apparent incongruity of the language of claim 1, it is submitted that the claim fails to delineate the subject matter that is regarded as the invention with the necessary degree of clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Furthermore, if the claimed antibody or antibody fragment need not bind “VE-cadherin”, but instead binds another structurally distinct polypeptide, which varies from “native VE-cadherin” by one or more amino acids within the first 15 N-terminal amino acids of the latter protein’s sequence, then, it is submitted that claim 1 fails to satisfactorily identify the particular protein(s) to which the claim is directed. Which protein is regarded as “native VE-cadherin”, and what is the amino acid sequence of that protein? Without knowing which protein is “native VE-cadherin”, and without knowing its amino acid sequence, it would not be possible to determine if another protein differs from “native VE-cadherin” as required by the claim. For these reasons, claim 1 inadequately delineates the metes and bounds of the subject matter that is regarded as the invention.

(b) Clams 7, 9, and 12 are indefinite because claim 7 uses the designation E4B9 as the sole means of identifying the claimed murine monoclonal antibody. The use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies.

Notably, amending claim 7 to include the depository accession number of a hybridoma producing the claimed murine monoclonal antibody would remedy this issue because deposit accession numbers are unique identifiers, which unambiguously define a given hybridoma and the monoclonal antibody produced by the hybridoma.

12. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

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The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipso verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). See also: *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to antibodies or fragments thereof that bind any one member of a genus of structurally and/or functionally varying "VE-cadherin" polypeptides, including but not limited to human VE-cadherin and mouse VE-cadherin.

Support for this broad interpretation of the claims is found throughout the specification, as filed. For example, the abstract of the disclosure describes the invention as antibodies, or immunologically active fragments thereof, specific for the N-terminal 15 amino acids of *any mammalian VE-cadherin*, which act as antagonists of

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VE-cadherin-mediated homophilic interactions between adjacent endothelial cells without adversely affecting normal vasculature.

In contrast, at paragraph [0007] of the published application, the specification merely describes "VE-cadherin" or "cadherin-5" as a polypeptide localized to intercellular junctions (adherens junctions) in cell-to-cell contacts, which has been described by the prior art (i.e., Lampugnani et al. (*J. Cell. Biol.* 1992; **118**: 1511-1522); Breviario et al. (*Arterioscler. Thromb. Vasc. Biol.* 1995; **15**: 1229-1239); Breier et al. (*Blood*. 1996; **87**: 630-641); and Lampugnani et al. (*J. Cell Biol.* 1995; **129**: 203-217). All of the cited publications but Breier et al. describe *human* VE-cadherin, whereas Breier et al. describes *mouse* VE-cadherin. None of these publications describe with particularity any other mammalian VE-cadherin.

Then, at paragraphs [0009] and [0010] of the published application, for example, the specification describes the claimed antibodies as inclusive of antibodies that bind "a VE-cadherin", which again is not necessarily human VE-cadherin, and not necessarily mouse VE-cadherin. Moreover, according to paragraphs [0012]-[0017], for example, the genus of polypeptides to which the claimed antibodies and fragments thereof bind include any polypeptide comprising any of the amino acid sequences set forth as SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, each of which is a mere fragment of a full-length polypeptide (i.e., human VE-cadherin or mouse VE-cadherin) or variant thereof. As such, the claims encompass antibodies capable of binding polypeptides having widely varying structures and/or functions.

Notably, SEQ ID NO: 2 and SEQ ID NO: 3 are fragments of the amino-terminus of domain 1 of mouse VE-cadherin and human VE-cadherin, respectively. These amino acid sequences differ by one amino acid.

The amino acid sequence of SEQ ID NO: 1, however, is not apparently a fragment of any known ortholog of human or mouse VE-cadherin; moreover, the amino acid sequence of SEQ ID NO: 1 does not appear to be a fragment of any other known polypeptide.

There is no disclosed correlation between any one particularly identifying (i.e., substantial) structural feature, which is shared by the genus of otherwise structurally

disparate polypeptides to which the claimed antibodies or fragments thereof bind, and any one particularly identifying functional feature, which is also shared by at least a substantial number of the members of the genus. As such, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of this genus of "VE-cadherin" polypeptides, as a whole; and consequently, the specification would not reasonably convey Applicant's possession of the claimed invention at the time application was filed.

Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes with requisite particularity the genus of polypeptides to which the claimed antibodies or fragments thereof, and absent such an adequate description of the polypeptides, there is no language that adequately describes the antibodies or fragments thereof that bind to these polypeptides and are capable of inhibiting the polypeptide-mediated adherens junction formation *in vitro*, but which do not affect paracellular permeability *in vitro* or vascular permeability *in vivo*. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen (e.g., human VE-cadherin), the written description would be met. However, as explained, the claims are not solely directed to antibodies or fragments thereof that bind well-characterized molecular targets (i.e., antigens), but rather to antibodies that bind

any of a plurality of structurally and/or functionally disparate polypeptides to inhibit formation of adherens junctions, which would otherwise occur.

Furthermore, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, e.g., the ability to specifically bind a polypeptide and inhibit its activity, does not provide an adequate written description of the genus. See *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the *polypeptides* to which the claimed antibodies or fragments thereof bind, it is impossible to make and use the claimed invention.

Arguably, even if the polypeptides to which the antibodies or fragments thereof bind are known or adequately described in the specification, although the skilled artisan could potentially screen candidate antibodies to identify those that bind "a VE-cadherin" and inhibit its function, so as to suppress the formation of adherins junctions without affecting paracellular permeability *in vitro* or vascular permeability *in vivo*, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere

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statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, "Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

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With regard to claim 9, as further explained below, the claim is directed to a genus of presumptively distinct hybridomas, which produce an antibody designated "E4B9". The claims are not necessarily directed to the hybridoma that has been described as a deposited hybridoma having the ATCC accession number PTA-1618; yet, the specification describes with particularity no other hybridoma that produces such an antibody. As such, the specification would not reasonably convey possession of the claimed invention at the time the application was filed.

13. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** the hybridoma deposited under ATCC accession number PTA-1618 and the antibody produced by said hybridoma, an antibody or antigen binding fragment thereof that binds human VE-cadherin or mouse VE-cadherin, a hybridoma producing said antibody that binds human VE-cadherin or mouse VE-cadherin, and a composition comprising any of said antibodies or antigen binding fragments thereof, **does not reasonably provide enablement for making or using** an antibody or antibody fragment that binds a site on any of a plurality of "VE-cadherin" polypeptides, an antibody or antibody fragment that binds a peptide or polypeptide comprising the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3, a hybridoma producing any of said antibodies or antibody fragments, or a pharmaceutical composition comprising any of said antibodies or antibody fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person

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skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the rejection of claims 1-6 and 8-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, the claims are directed to antibodies or antibody fragments that bind to any of a plurality of structurally and/or functionally disparate "VE-cadherin" polypeptides, which have not been adequately described, so as to reasonably permit the skilled artisan to immediately envision, recognize or distinguish at least most of these polypeptides. For this very same reason, it is submitted that the specification would not reasonably enable the skilled artisan to make the polypeptides, as one cannot make that which has not been described. Because the skilled artisan could not make the polypeptides to which the claimed antibodies or fragments thereof bind, the skilled artisan could not make or use the antibodies or fragments thereof without undue and/or unreasonable experimentation.

Furthermore, because the claimed antibodies and fragments thereof bind to such structurally disparate polypeptides (e.g., polypeptides comprising the amino acid sequence of SEQ ID NO: 1, a mere fragment of a variant of human VE-cadherin and mouse VE-cadherin), it is submitted that, even were the skilled artisan reasonably enabled to make antibodies that bind these various polypeptides, the skilled artisan could not use those antibodies without undue and/or unreasonable experimentation. Because the polypeptides to which these antibodies or fragments thereof bind differ so substantially in structure, it is expected that their biologic functions and specific activities will vary widely. It follows therefore that many, if not most, of these polypeptides will not have a function similar to that of either mouse VE-cadherin or human VE-cadherin, and may not mediate formation of adherens junctions to provide or otherwise affect paracellular or vascular permeability.

It is submitted that the specification would only be sufficient to enable the skilled artisan to make and use an antibody or antigen binding fragment thereof that binds to mouse VE-cadherin or human VE-cadherin, as opposed to an ortholog of either or any other variant thereof.

This position is supported, for example, by the teachings of Skolnick et al. (*Trends Biotechnol.* 2000; **18** (1): 34-39). Skolnick et al. discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science* 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn,

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utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the antibodies, which possibly fall within the scope of the claims, the skilled artisan could not recognize which of these could be used in the manner described in the specification because it would not be possible to reliably predict whether the polypeptide to which the antibody binds functions similarly to mouse VE-cadherin or human cadherin, and which would not.

Furthermore, although the polypeptides to which the claimed antibodies or antibody fragments bind are disclosed as comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, the specification does not describe any of these amino acid sequences as essential to any one particular activity or biologic function shared by each of the structurally different polypeptides. As noted above, SEQ ID NO: 1 appears to be a novel amino acid sequence; and there are no polypeptides known or described in the specification, which comprise this particular sequence. Additionally, the specification does not teach which amino acids in the about first 15 N-terminal amino acids of domain 1 of a native VE-cadherin sequence can be replaced, and by which other amino acids, or deleted without a loss of such an activity. Again, as evidenced by the teachings of Skolnick et al. and Bowie, for example, the skilled artisan cannot accurately and reliably predict whether a given homologue of a particular protein known to have a certain activity (e.g., human VE-cadherin) will also have that same activity. The skilled artisan cannot reliably and accurately predict the functional and structural consequences of amino acid differences; but the more structurally disparate a given protein, the less likely the protein will share the function of structurally related proteins having known functions. Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of such sensitivity, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of

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aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

Consistently, Luque et al. (*Biochem.* 2002 Nov 19; **41** (46): 13663-13671) reported that substitution of a single highly conserved amino acid in baculovirus *Orgyia psuedotsugata* Op-IAP and *Drosophila* DIAP1 abolishes the function of the proteins, as defined by their ability to bind apoptosis stimulators, including *Drosophila* Hid and mammalian Smac/DIABLO; see entire document (e.g., the abstract). Although the amino acid replaced is highly conserved and might therefore have been reasonably expected to be essential to the function of the protein, because the inhibitor of apoptosis proteins have more than one specific activity, some residues, which although conserved, may not be important to specific activities, whereas others are. The skilled artisan cannot predict which conserved amino acid residues are critical to which specific activities of such multifunctional proteins. For example, Vucic et al. (*J. Biol. Chem.* 1998 Dec 18; **273** (51): 33915-33921) performed a mutational analysis of baculovirus inhibitor of apoptosis Op-IAP and found that, although most of the conserved amino acid residues in the BIR2 motif were revealed to be essential to the protein's ability to inhibit apoptosis, most of these conserved residues were not required for binding to Hid; see entire document (e.g., the abstract). A region at the carboxy-proximal end of BIR2 was essential for binding to Hid (apoptosis). Vucic et al. disclose that these results show that binding to Hid is necessary but not sufficient to block Hid-induced apoptosis (abstract). Thus, while it is possible to determine which amino acids residues are conserved in various different family members, it is not possible to predict which of these conserved residues are critical to the various different functions of a multifunctional protein.

Echoing this fact, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid

change may be sufficient to cause the acquisition of a new ligand binding specificity as well as to suppress recognition of a previous ligand, extending observations by others who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA*. 2004 Jun 22; **101** (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be 34%  $\pm$  6% (abstract); that is, 34% of random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein (i.e., the so-called "x factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, Lazar et al., for example, shows that even a single, conservative amino acid change can cause substantial changes in the activity of a protein, so it is evident

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that the skilled artisan cannot predict the functional consequences of amino acid substitutions and must determine those consequences empirically; and since Guo et al. shows that amino acid substitutions are remarkably likely to cause inactivation of the protein, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given variant of a protein can be used in the same manner in which the protein having a known function is used.

For these reasons, even were the disclosure sufficient to reasonably enable the skilled artisan to *make* the polypeptides to which the claimed antibodies and antibody fragments bind, the skilled artisan could not reasonably use those antibodies or fragments thereof in a manner consistent with the asserted utility of the particularly disclosed antibody or fragment thereof that binds mouse VE-cadherin and/or human VE-cadherin. Again, the skilled artisan cannot predict whether the polypeptides to which the claimed antibodies or fragments thereof will function to mediate the formation of adherens junctions, and consequently the skilled artisan cannot predict upon any reasonable and factual basis whether the antibody or fragment thereof will be capable of inhibiting formation of adherens junctions with or without affecting paracellular or vascular permeability.

Then, with regard to the claimed pharmaceutical compositions, which are disclosed as useful to inhibit angiogenesis or tumor metastasis, because the skilled artisan cannot predict upon any reasonable and factual basis whether the antibody or fragment thereof will be capable of inhibiting formation of adherens junctions with or without affecting paracellular or vascular permeability, the skilled artisan cannot predict whether any of the claimed antibodies or fragments thereof are therapeutically effective, when administered to a patient, to inhibit angiogenesis or tumor metastasis.

To the extent that the claims are directed to the disclosed antibody or fragment thereof that is produced by the deposited hybridoma, it is noted that the exemplary use of the antibody to inhibit angiogenesis or tumor metastasis is limited to mouse models.

As such, it is submitted the teachings of the specification cannot be extrapolated to provide sufficient enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with claims directed toward

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pharmacologic and clinical useful products. It is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science*. 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to be better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Saijo et al. (*Cancer Sci*. 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Kelland (*Eur. J. Cancer*. 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Admittedly the use of mouse xenografts for evaluating therapeutic efficacy of drugs for treating humans is a well established practice; nonetheless, the results of preclinical studies using such models for human disease should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that

"[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer*. 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

This position is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer*. 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skepticism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Most recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show

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positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Claim 9 is drawn to a hybridoma producing an antibody, which according to claim 7 is the murine monoclonal antibody E4B9.

At page 9, lines 14-17, the specification refers to a biological deposit of a hybridoma having the ATCC accession number PTA-1618, which is described as a hybridoma that produces rat anti-murine VE-cadherin E4B9.

Nevertheless, claim 9 is not necessarily directed to this hybridoma, which has been deposited under ATCC accession number PTA-1618; rather, the claim is broadly but reasonably drawn to any of a genus of hybridomas that produce a monoclonal antibody according to claim 7, which may include but is not limited to the deposited hybridoma.

It is unclear if the hybridomas to which claim 9 is directed, having the exact structural and chemical identity of the deposited hybridoma or producing an antibody having the exact structural and chemical identity of the antibody to which the claim refers, are known and publicly available, or can be reproducibly produced or isolated without undue experimentation. Clearly, without access to the hybridomas to which the claim is directed, it would not be possible to practice the claimed invention.

If the deposited hybridoma is the only hybridoma considered to be the invention, then Applicant may remedy this issue by amending claim 9 to recite a limitation requiring the hybridoma to be the hybridoma deposited under ATCC accession number PTA-1618.

Otherwise, if the invention is considered to include additional hybridomas that produce such an antibody, suitable deposits of such other hybridomas for patent purposes is suggested, since the deposits would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the

grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Furthermore, the specification should be amended to provide requisite information regarding such deposits (i.e., specific reference to the deposited material by the name of the depository and its accession number, which further provides the depository's address and the date the deposit was made). See 37 C.F.R. § 1.809 (d).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 1-6 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lampugnani et al. (*J. Cell Biol.* 1992 Sep; **118** (6): 1511-1522) (of record; cited by Applicant).

Claims 1-6 and 12 are drawn to an antibody or antibody fragment that specifically binds to a peptide comprising the amino acid sequence of SEQ ID NO: 3, a hybridoma producing said antibody, or a composition comprising said antibody and a pharmaceutically acceptable carrier or diluent (e.g., water).

Lampugnani et al. teaches mouse monoclonal antibodies that specifically bind to human VE-cadherin; see entire document (e.g., page 1512, column 1). Lampugnani et al. teaches a fragment of these antibodies; see, e.g., page 1512, column 1. Lampugnani et al. teaches hybridomas producing these antibodies; see, e.g., page 1512, column 1. Lampugnani et al. teaches compositions comprising these antibodies and a pharmaceutically acceptable carrier or diluent (e.g., water); see, e.g., page 1512, column 2. Additionally, Lampugnani et al. teaches a polyclonal rabbit pan-cadherin antiserum, which comprises antibodies that specifically bind to human VE-cadherin; see, e.g., page 1512, column 1.

Although Lampugnani et al. does not expressly teach the disclosed antibodies or fragments thereof are capable of inhibiting VE-cadherin mediated adherens junctions formation without exerting significant or substantial effect on paracellular vascularity *in vitro* and/or vascular permeability *in vivo*, such specific properties of antibodies are deemed inherent properties of the claimed antibodies or fragments thereof. Accordingly, because the disclosed antibodies specifically bind to a peptide comprising the amino acid sequence of SEQ ID NO: 3, the prior art teaches antibodies that are

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structurally and functionally indistinguishable from the claimed antibody or antibody fragment. Notably, the Office does not have the facilities for examining and comparing Applicant's product with a product disclosed by the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is different from the product taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Furthermore, for these same reasons and absent a showing otherwise, the disclosed antibodies or fragments thereof are substantially non-toxic when administered to an animal or more particularly a mammal and are deemed the same as the antibodies or fragments thereof, which are capable of inhibiting angiogenesis or tumor metastasis and/or capable of inhibiting formation of new adherens junctions formation without disturbing existing adherens junctions.

16. Claims 1-6 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Corada et al. (*Proc. Natl. Acad. Sci. USA*. 1999 Aug; **96**: 9815-9820) (of record; cited by Applicant).

Claims 1-6 and 12 are drawn to an antibody that specifically binds to a VE-cadherin at a site within the about first 15 N-terminal amino acids of domain 1, which site differs by substitution of one amino acid from the corresponding site of a native VE-cadherin, or alternatively to an antibody or fragment thereof that specifically binds to a peptide comprising the amino acid sequence of SEQ ID NO: 2, a hybridoma producing said antibody, or a composition comprising said antibody and a pharmaceutically acceptable carrier or diluent (e.g., water).

The about first 15 N-terminal amino acids of domain 1 of mouse VE-cadherin differ from the about first 15 N-terminal amino acids of domain 1 of human VE-cadherin by one amino acid substitution. *Cf.* SEQ ID NO: 2 and SEQ ID NO: 3, as disclosed in

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the instant application by, e.g., Figure 2, which correspond to the amino-terminal sequences of mouse VE-cadherin and human VE-cadherin, respectively.

Corada et al. teaches rat monoclonal and rabbit polyclonal antibodies that specifically bind to mouse VE-cadherin; see entire document (e.g., page 9815, column 2). Corada et al. teaches a fragment of a monoclonal antibody having this binding specificity; see, e.g., page 9815, column 2. Corada et al. teaches compositions comprising these antibodies and a pharmaceutically acceptable carrier or diluent (e.g., water); see, e.g., page 9816, column 1.

Although Corada et al. does not expressly teach that the disclosed polyclonal antibody binds mouse VE-cadherin at a site in the about first 15 N-terminal amino acids of domain 1 of the polypeptide, absent a showing otherwise, the polyclonal antiserum comprises a species of antibody capable of binding to this site. This conclusion is reasonable because a polyclonal antiserum produced against a recombinant fragment of mouse VE-cadherin consisting of the extracellular domain is expected to comprise antibodies that bind to any and all epitopes (i.e., antigenic determinants) of such a polypeptide.

Although Corada et al. does not expressly teach each of the disclosed antibodies or fragments thereof are capable of inhibiting VE-cadherin mediated adherens junctions formation without exerting significant or substantial effect on paracellular vascularity *in vitro* and/or vascular permeability *in vivo*, such specific properties of antibodies are deemed inherent properties of the claimed antibodies or fragments thereof, unless it has been established that the antibodies lack such properties. Corada et al. teaches monoclonal antibodies BV13 and BV14 bind distinct epitopes of mouse VE-cadherin, and while BV13 exerts significant or substantial effects upon vascular permeability *in vivo*, BV14 does not; see, e.g., page 9816, column 2; and page 9817, Figure 5. Otherwise, because the other disclosed antibodies specifically bind to a peptide comprising the amino acid sequence of SEQ ID NO: 2, the prior art teaches antibodies that are structurally and functionally indistinguishable from the claimed antibody or antibody fragment; and as explained above, the Office does not have the facilities for examining and comparing Applicant's product with a product disclosed by the prior art in

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order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed product. Again, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is different from the product taught by the prior art.

Furthermore, Corada et al. administers one or another of the disclosed antibodies or antibody fragments to mice but does not report that such treatments were toxic, suggesting that the antibodies or fragments thereof are substantially non-toxic in a mammal. Therefore, absent a showing otherwise, the disclosed antibodies or fragments thereof are substantially non-toxic when administered to an animal or more particularly a mammal.

For these same reasons, again absent a showing otherwise, one or more of the disclosed antibodies or fragments thereof is deemed the same as the claimed antibody or antibody fragment capable of inhibiting angiogenesis or tumor metastasis and/or capable of inhibiting formation of new adherens junctions formation without disturbing existing adherens junctions.

### ***Conclusion***

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent Application No. 2003/0206902 A1 teaches antibodies or antibody fragments that bind human VE-cadherin and/or mouse VE-cadherin, including polyclonal and monoclonal antibodies (e.g., monoclonal antibodies Cad5, BV9, BV6, BV13, TEA, and Hec1.2); additionally, U.S. Patent Application No. 2003/0206902 A1 teaches N-terminus of the cadherins is important in regulating homotypic cell-cell interactions, and suggests that anti-mouse or human VE-cadherin monoclonal antibodies that have no effect upon vascular permeability in normal tissues are selected for further testing in angiogenesis and tumor models. Breier et al. (of record; cited by Applicant) teaches polyclonal antibodies capable of specifically binding

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to peptides comprising SEQ ID NO: 2. Each of Lampugnani et al. (*J. Cell. Biol.* 1992; **118**: 1511-1522), Navarro et al. (*J. Cell Biol.* 1998 Mar 23; **140** (6): 1475-1484), Bach et al. (of record; cited by Applicant), Yang et al. (*Am. J. Pathol.* 1999 Sep; **155** (3): 887-895), Bach et al. (*J. Biol. Chem.* 1998 Nov 13; **273** (46): 30719-30728), U.S. Patent No. 5,646,250 A (Suzuki et al.), WO 99/57149 A2 (Blaschuk et al.), and U.S. Patent Application Publication No. 2005/222037 A1 (Blaschuk et al.) teach monoclonal and/or polyclonal antibodies capable of specifically binding to peptides comprising SEQ ID NO: 2 and/or SEQ ID NO: 3.


Other art made of record, but not relied upon, is considered pertinent to Applicant's disclosure. Each of May et al. (*Blood*. 2005 June 1; **105** (11): 4337-4344), Liao et al. (*Cancer Res.* 2000 Dec 15; **60**: 6805-6810), and Corada et al. (*Blood*. 2002 Aug 1; **100** (3): 905-911) teach monoclonal antibodies that bind peptides comprising SEQ ID NO: 2 and/or SEQ ID NO: 3.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Stephen L. Rawlings, Ph.D.  
Examiner  
Art Unit 1643

slr  
January 16, 2007